National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Ustekinumab for treating moderately to severely active Crohn's disease after prior therapy

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit

Section	Consultee/Commentator	Comments [sic]	Action
Appropriateness	British Society for Gastroenterology	Fully appropriate	Comment noted.
	Crohn's and Colitis UK	We consider it appropriate and timely to refer this topic to NICE for appraisal, as this technology offers the potential to meet a growing unmet need for those with Crohn's Disease for whom other available treatment options have failed or are not suitable. Conventional therapies for Crohn's Disease are suboptimal - anti-TNF therapy produces remission in approximately one third of patients with many losing response over time. A significant proportion of these patients continue to experience flares or chronic symptoms as well as the adverse effects of nonspecific anti-inflammatory agents such as corticosteroids (side effects of which include thinning of bones, muscle and skin).	Comment noted.
	Janssen	Janssen believes this is an appropriate topic to refer to NICE for appraisal	Comment noted.
	Napp Pharmaceuticals	Yes	Comment noted.

Section	Consultee/Commentator	Comments [sic]	Action
	Limited		
Wording	British Society for Gastroenterology	Yes	Comment noted.
	Janssen	Yes, it does.	Comment noted.
	Napp Pharmaceuticals Limited	Yes	Comment noted.
Timing Issues	British Society for Gastroenterology	I understand Ustekinumab may have a licence in early 2017, so the timing seems appropriate.	Comment noted.
	Crohn's and Colitis UK	Given the unmet need, the likely timeframe for consideration and ultimate access to the treatment for patients with Crohn's Disease, we would like to see this appraisal referred and undertaken in as timely a manner as possible.	Comment noted.
	Janssen	The timing of this appraisal is appropriate.	Comment noted.
	Napp Pharmaceuticals Limited	Treatment options are available, therefore prioritisation should be governed by NICE scheduling in-line with its normal processes.	Comment noted.
Background information	British Society for Gastroenterology	Appropriate	Comment noted.
	Crohn's and Colitis UK	This information is accurate, but we do not consider it to be complete as it does not reflect the impact that the condition has on quality of life. Social function may be substantially impaired in terms of inability to work, attend school, participate in leisure activities, or have intimate relationships. Emotional function may be affected by difficulty in coping with personal lives and feelings of anger,	Comment noted. The background section is only intended to provide a brief description of the disease and current management options.

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		embarrassment, frustration, sadness, and fears of needing surgery or developing cancer. Additionally, most reports indicate that stress may be involved in triggering relapse. Whether patients have active or quiescent IBD, they often report symptoms of profound fatigue. Studies have demonstrated that fatigue measurement scores in patients with IBD are comparable to scores reported in cancer patients. An individual with Crohn's states: "Crohn's Disease is an incurable and relapsing condition, which blights my life. I am an experienced professional teacher and a trustee of a local charity but my ability to contribute to my community, to wider society, and to pay my taxes, is limited by the impact of the disease. It forces me to work part-time when I would otherwise work full-time and I have regular episodes of sick-leave, roughly every 12-18 months. The latest period of sick-leave will last six weeks, which is a burden on my employers. The impact on my family and social life is huge. I haven't been able to travel abroad for over two years." Additionally, it should be noted that the number of people with Crohn's Disease is increasing rapidly, especially in the paediatric population. While this technology is not currently licensed for use in the paediatric population, this emphasises the need for effective treatment options for young adults.	No changes have been made to the scope.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
The technology/ intervention	British Society for Gastroenterology	yes	Comment noted.

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	Napp Pharmaceuticals Limited	Yes	Comment noted.
Population	British Society for Gastroenterology	There might be a case for considering the effect in patients who have had exposure to anti Integrin treatments (Vedolizumab) separately. There will be the question as to whether patients might be able to have anti TNF, then anti Integrin and then anti IL-23 (ustekinumab) treatment.	Comment noted. Consideration of whether patients have previously been treated with TNF inhibitors has been included as a subgroup analysis, if the evidence allows.
	Napp Pharmaceuticals Limited	Yes	Comment noted.
Comparators	British Society for Gastroenterology	Yes	Comment noted.
	Crohn's and Colitis UK	It should be noted in any comparison of treatments, Crohn's Disease varies significantly in its pattern and severity between individuals. It can also vary in the same individual due to its unpredictable and relapsing nature. Likewise, response to and suitability of different treatments can vary between individuals.	Comment noted. To account for some of the heterogeneity of the disease, consideration of the location of the Crohn's disease has been included as a subgroup analysis, if the evidence allows.
	Napp Pharmaceuticals Limited	Yes When referring to infliximab, please include all commercially available infliximab brands i.e. Remsima®, Inflectra® and Remicade®. It will be important to include the biosimilar NHS tender prices to ensure that the most appropriate cost-effectiveness is determined.	Comment noted. The economic analysis section of the scope now states that the availability and cost of biosimilars should be taken into consideration. This will include all commercially available brands of biosimilars.

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Outcomes	British Society for Gastroenterology	Measures of mucosal healing would add to the outcome measures	Comment noted. Mucosal healing has been added to the scope as an outcome.
	Crohn's and Colitis UK	Outcomes that are important to patients should be considered as these may not correlate with clinical outcomes.	Comment noted.
	Napp Pharmaceuticals Limited	Yes	Comment noted.
Economic analysis	British Society for Gastroenterology	Cost effectiveness analysis is difficult for the longer term use of this treatment. Previous NICE appraisals have suggested a 12 month treatment period with re-assessment rather than automatic continuation. While there is not much evidence to support this approach most clinicians would not expect to use these agents for an indefinite duration.	Comment noted.
	Napp Pharmaceuticals Limited	To ensure that all relevant comparators are included in the analysis the tender price of biosimilar infliximab should be taken into account. Recent NICE MTAs have included both the NHS list price and the tender price for biosimilar infliximab. The manufacturer could carry out sensitivity analysis to include a range of potential discounted infliximab prices.	Comment noted. The economic analysis section of the scope now states that the availability and cost of biosimilars should be taken into consideration.
Equality	British Society for Gastroenterology	No equality issues identified	Comment noted.
	Crohn's and Colitis UK	Inadequate response to medical treatment can lead to surgery, which can have a significant impact on fertility, primarily for women, so this should be considered in terms of potential gender discrimination. This impact is	Comment noted.

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		exacerbated given the peak diagnosis period in the teens and twenties and surgery also carries particular issues for those following certain religious practices.	
	Napp Pharmaceuticals Limited	The scope does not exclude any people protected by the equality legislation who fall within the patient population for which the treatment may be licensed.	Comment noted.
Other considerations	British Society for Gastroenterology	none	Comment noted.
	Janssen	We propose the inclusion of the following text: "According to label indication and the evidence available, the following patient populations should be considered: People who have not previously received a TNF-α antagonist; People for whom at least one TNF-α antagonist has failed; People for whom TNF-α antagonists are not suitable because of intolerance or contraindication."	Comment noted. The suggested text has been incorporated into the other considerations section of the scope to reflect the need to consider previous treatments that patients have received.
Innovation	British Society for Gastroenterology	Yes, ustekinumab is novel, it is the first of potentially several antibody treatments targeted at the IL23 pathway. It is innovative with a major potential to change practice.	Comment noted.
	Crohn's and Colitis UK	As ustekimumab is derived from a newly engineered cell line, and has a different mode of action from currently available drugs for Crohn's, we consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefit. The aim of the treatment is to induce and maintain	Comments noted. Consideration will be given to those factors which are not already captured within the economic modelling presented by the company in

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		remission in adult patients with moderately to severely active Crohn's Disease who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a tumour necrosis factor alpha (TNFα) antagonist. For those in this position, the potential value of the treatment is significant and could restore quality of life to the individual and avert further complications and surgery. Averting the need for surgery is important as, due to the nature of the condition, and the fact that it can occur anywhere in the gastrointestinal tract, having surgery once does not preclude the potential need to have surgery again. Surgery carries many potential costs, both to the individual and to the NHS. It can have an associated profound psychological and social impact, for example, in terms of body image and self-esteem. For those who are facing this at an age when they have just begun to form relationships and do not yet have a family, this can be especially difficult. The inflammation in Crohn's Disease may lead to strictures (narrowing) of the bowel resulting in abdominal pain caused by partial blockage. Severe cases may lead to life-threatening complications such as complete blockage or perforation of the bowel. Crohn's Disease is often associated with anal problems such as fissure, tags, abscess and fistulas (abnormal channels between the bowel and other parts of the body). Therefore, further innovative drugs are necessary to reduce additional medical indications which significantly reduce quality of	its submission.

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		life. The introduction of a new drug treatment increases treatment options for people with Crohn's Disease who do not respond to conventional treatment, providing opportunities to help more patients stabilise their condition and restore quality of life. In terms of costs to the NHS, this could include: Ongoing stoma care and appliances Potential fertility treatment for young women after surgery Hospital costs for the treatment of infections and other complications Psychological support – IBD-related surgery or hospitalisation is associated with a significant risk for depression and anxiety. Repeated surgery can lead eventually to short bowel syndrome and the potential for total or partial lifelong dependence on parenteral nutrition. An individual with living with Crohn's Disease states: "No amount of surgery can remove Crohn's due to its ability to occur anywhere in the GI tract - in fact surgery tends to make matters worse as sections repeatedly get removed till you end up with lifelong symptoms, and expenses involved in treatment, caused by a shortage of bowel. I have been in that situation for 15 years having had two major surgeries and had every drug available, yet still the illness persists. My outlook at present is to be condemned to never working again, having no social life, depression and having a diet limited to less than ten food items. My current intake of 16,376 tablets and 30	

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		injections every year will just roll over year after year after year unless a new drug treatment is successful."	
	Janssen	Ustekinumab offers an alternative mode of action compared to anti-TNF agents and vedolizumab and therefore offers a treatment alternative where prior therapies are inappropriate or are ineffective. Ustekinumab has a rapid induction through IV dosing, leading to a more rapid onset of effect. Ustekinumab has convenient maintenance dosing through SC administration and patients with lower inflammatory burden may benefit from the less frequent dosing schedule with ustekinumab (every 12 weeks) compared to adalimumab (every 2 weeks) or infliximab and vedolizumab (every 8 weeks). This thereby reduces the treatment burden for patients.	Comments noted.
	Napp Pharmaceuticals Limited	The technology may offer an alternative for patients who fail or may not be suitable for existing first and / or second-line treatments.	Comment noted.
Questions for consultation	British Society for Gastroenterology	Questions for consultation Have all relevant comparators for ustekinumab been included in the scope? **Yes.** Which treatments are considered to be established clinical practice in the NHS for moderately to severely active Crohn's disease? **Steroids (prednisolone), immunosuppression (azathioprine, MTX), anti TNF antibodies and anti Integrin antibodies (Vedolizimab).**	Comments noted. The treatments listed reflect the treatments currently included in the scope.

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		Are the outcomes listed appropriate? **Yes, but you could add mucosal healing.** Are there any subgroups of people in whom ustekinumab is expected to be more clinically effective and cost effective or other groups that should be examined separately? **Ileal, colonic and perianal Crohn's may all have different responsiveness to Ustekinumab.** Where do you consider ustekinumab will fit into the existing NICE pathway for Crohn's disease? **After anti TNF antibodies, infliximab and / or adalimumab.** NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope: • could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which ustekinumab will be licensed; **No** • could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology; **No** • could have any adverse impact on people with a	Mucosal healing has been added to the scope. To reflect the difference in responsiveness treatments, consideration of the location of the Crohn's disease has been included as a subgroup analysis, if the evidence allows.

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		particular disability or disabilities. **No** Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts. Do you consider ustekinumab to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)? **Yes, as above it is novel and may have substantial impact.** Do you consider that the use of ustekinumab can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation? **Yes, the use of this agent may allow mucosal healing and thus help some patients avoid colectomy and permanent ileostomy. The benefits of this are hard to quantify but real.** Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits. **Data is limited but the full reports of the phase 3 trials should be available to the committee.**	

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	Napp Pharmaceuticals Limited	Where do you consider ustekinumab will fit into the existing NICE pathway for Crohn's disease? **For patients unable to achieve remission on first / second line treatments or for those who have failed second-line treatment.**	Comment noted.

The Royal College of Physicians formally endorses the response submitted by the British Society of Gastroenterology.

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

Department of Health
Merck Sharp and Dohme
Royal College of Nursing
Pfizer